REMARKS

Claims 3-17 are pending. New claim 18 has been added.

Support for the amendment to claims 3 and 4 can be found in the Specification on page 5, lines 5-6, and in Example 1, page 27, line 24 to page 28, line 24.

The dependency of claim 5 has been changed.

Support for new claim 18 can be found in claim 12 and in the Specification on page 27, lines 13-17.

No new matter has been added.

Rejections Under 35 USC §112, first paragraph

The Examiner has rejected claims 3-17 as failing to comply with the written description requirement. Specifically, the Examiner states "Recourse to the specification does not define the expression 'applying across a wound in the surface of the skin'" and contends that this is new matter. Applicants respectfully traverse.

Written description does not require *in haec verba* statements to appear in the Specification. MPEP 2163 B. The claim limitations must be supported in the Specification through express, implicit, or inherent disclosure. *Ibid.* To comply with the written description requirement an applicant must convey with reasonable clarity to ***those skilled in the art*** that ... her or she was in possession of the invention and that the invention is whatever is now claimed (emphasis added). MPEP 2162.02. Furthermore, the MPEP states "Prior to determining whether the disclosure satisfies the written description requirement for the claimed subject matter, the examiner should ***review*** the claims and ***the entire specification***..." (emphasis added). MPEP 2163 II A 2. "Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art." *Ibid.*

Applicants point out that the title of the invention is "Use Of Hyaluronic Acid Derivatives In Pharmaceutical Preparations And Biomaterials For The Prevention And Treatment Of Cutaneous Scars." Hence the title itself indicates that the scars to be prevented and treated occur on the skin since "cutaneous" is defined as "pertaining to the skin" (In *Taber's Cyclopedic Medical Dictionary*, Edition 18, copyright 1997, Clayton L.

Thomas (ed.), F.A. Davis Company, Philadelphia). The first sentence of the Background section of the Specification states "A cutaneous scar is the outcome of the repair processes that restore the continuity of damaged skin." If the reference to "repair processes that restore the continuity of damaged skin" in this sentence were not sufficient to indicate that a wound was present, the first sentence of the second paragraph of the Background section makes this clear. It states "Normal wound healing in response to tissue injury involves several integrated processes...." Furthermore, the first sentence of the Detailed Description of the Invention section states "The aim of the present invention is to provide biomaterials containing at least one hyaluronic acid derivative which is efficacious in reducing the area of skin affected by scarring. Applicants assert that from this information alone one of skill in the art would understand that the claimed hyaluronic acid derivatives are topically placed on the skin across the wound. This is also supported by the experiment described in Example 1. Here, animals suffering cutaneous wounds were treated with either a partial benzyl ester of hyaluronic acid in the form of a non-woven fabric or simply with hyaluronic acid applied across the wound site. Topical application of non-woven fabrics and direct application of a compound across a wound site is standard in the art. As a consequence, the Specification does, indeed, provide more than sufficient description so that one skilled in the art would understand that the claimed biomaterials are used by "applying across a wound in the surface of the skin."

In view of the above, Applicants respectfully request reconsideration and removal of the rejections.

Rejections Under 35 USC § 112, second paragraph

The Examiner has rejected claim 4 for failing to set forth any steps involved in the use/process claimed. Applicants amended claim 4 to comply with US format for method of treatment claims, thereby overcoming the rejection.

Rejections Under 35 USC § 103

WO 99/04828 ('828)

The Examiner has rejected claims 3-7 as being obvious over WO 99/04828 ('828) in view of WO 94/17837 ('837). The Examiner contends that the '828 patent publication

discloses hyaluronic acid derivatives that are (1) esterified with alcohols, (2) auto-cross linked esters, (3) cross-linked hyaluronic acid compounds, (4) hemiesters of succinic acid, (5) N-sulphated derivatives of hyaluronic acid and (6) amid derivatives. The Examiner also contends that these listed hyaluronic acid derivatives can be formulated as gels and pharmacologically active substances can be added. Lastly, the Examiner contends that these hyaluronic acid-based compositions are used to treat formation of post-surgical adhesion and scar formation.

The Examiner acknowledges that '828 does not specifically teach skin scar treatment. He tries to fill this void with the teachings of the '837 reference. Specifically, the Examiner contends that '837 teaches a multilayer non-woven material comprising a surface layer which comes into contact with the skin and one or more other layers which do not come into contact with the skin, wherein said surface layer which comes into contact with the skin is at least one derivative of hyaluronic acid. The Examiner also contends that the reference discloses that the materials are used in dermatology such as treating skin pathologies. From this the Examiner concludes that it would have been obvious for a skilled artisan to have used hyaluronic acid ester for the treatment of scarring by using the composition of '828. Applicants respectfully traverse.

Applicants first point out that the **'837 and '828 references teach away** from the instant invention. '837 states that hyaluronic acid derivates and/or their mixtures have (1) poor mechanical characteristics when wet due to its tendency to form a gel when in contact with aqueous fluids such a physiological fluids, (2) high cost and (3) excessively high vapour transmission values (see Description of Related Art). '837 then states "These drawbacks are particularly significant in cases where poor exudate production is present" (emphasis added). As a rule, the skin scarring process, especially the normotrophic scarring process does not depend on or produce exudate; that is there is poor exudate production. "Exudate" is defined as "accumulated fluid in a cavity, matter that penetrates through vessel walls into adjoining tissue, or an oozing of pus or serum" (Tabor's Cyclopedic Medical Dictionary, Edition 18, 1997, Clayton Thomas (*ed.*), F.A. Davis Company, Philadelphia). Thus, scarring of the skin is significantly different from the case in most surgical situations where the amount of exudate oftentimes requires a drain for

removal. As a consequence, the type of post-surgical adhesion "scar" referred to in the '828 reference is not comparable to skin scarring, especially normotrophic scarring.

Furthermore, the claims are now directed to normotrophic scarring. Normotrophic scarring results from the normal biologic process of wound repair in the skin and is a natural part of the healing process. It is a normal response to tissue injury with firm tissue limited to the original wound border (see page 2 of the Specification). It is not directed to abnormal scarring such as hypertrophic scarring.

The healing process is a very complicated process of tissue repair that results from phases as described in Wokalek and Ruh (1991, J Biomaterials Applications 5: 338-362; attached). Pages 354-357 discuss scar formation where Wokalek and Ruh point out "fibroblasts with contact specialization ... are involved in wound contraction and cell adhesion by cell-cell and cell-extracellular matrix contacts. In addition ... the adhesion and its pulling property of the modified fibroblasts is part of the remodeling of the newly formed matrix during wound healing." That is, in order for wound healing to occur, the adhesion process must occur. This would appear to be contrary to the teachings of the prior art, such as the '828 reference, which teach that hyaluronic acid derivatives prevent adhesion. In other words, one skilled in the art would not be motivated to use hyaluronic acid derivatives known to prevent adhesion for treatments that require adhesion to be present.

In addition, as the Examiner has stated, the '837 reference is minimally directed to use of its materials for skin pathologies. Cutaneous scars, especially normotrophic scars, are not skin pathologies. As evidenced by the chapter XXIV Skin Diseases (Frank Parker (1988) pages 2304-2342 *In*: Cecil Textbook Of Medicine, Wnygaarden and Lloyd (*eds.*), Harcourt Brace Jovanovich, Inc, Philadelphia; attached) and the discussion above, wound healing is a normal process. While a defect in the closure of the skin produces a scar, this, in and of itself, is not a pathology. Scarring does not fall under any of the major types of dermatological pathologies listed in Tables 531-3, 532-1, 534-1, 534-4, 534-6, 534-9 and 534-10. Scarring may, or may not, be associated with a few pathologies such as *Lupus erythematesus*. But the teaching of the '837 reference says nothing about *Lupus erythematesus* or any other type of pathology associated with cutaneous scarring. In fact, aside from some very vague references to fields of medicine such as dermatology,

surgery, neurosurgery, orthopaedics, etc., '837 makes no treatment statements whatsoever. As a consequence, one skilled in the art would not be motivated to look to this reference for guidance as to how to reduce normotrophic scarring.

In view of the above, Applicants respectfully request reconsideration and removal of the rejections.

WO 97/07833 ('833)

The Examiner has rejected claims 3-10 and 12-17 as being obvious over WO 97/07833 ('833) in view of WO 94/17837 ('837). The Examiner contends that the '833 publication discloses the following set of hyaluronic acid derivatives: (1) hyaluronic acid esterified with alcohols, (2) auto-crosslinked esters and (3) crosslinked hyaluronic acid compounds. The Examiner notes that the hyaluronic acid derivatives can be formulated as gels and additional pharmacologically active substances can be added. He also contends that '833 teaches hyaluronic acid derivatives used for prevention of post-surgical adhesion and states that '833 defines "adhesion" as a permanent scar that connects to adjacent surfaces.

The Examiner's contentions about the '827 reference appear above and are not repeated here. The Examiner then concludes that while the '833 reference does not specifically teach skin scar treatment, Applicants respectfully traverse.

Applicants first note that claim 3 is directed to treatment of normotrophic scarring on the skin. As discussed above, the skin scarring process, especially the normotrophic scarring process, typically does not depend on or produce exudate. "Exudate" is defined as "accumulated fluid in a cavity, matter that penetrates through vessel walls into adjoining tissue, or an oozing of pus or serum" (Tabor's cyclopedic Medical Dictionary, Edition 18, 1997, Clayton Thomas (*ed.*), F.A. Davis Company, Philadelphia). This is significantly different from the case in most surgical situations where the amount of exudate oftentimes requires a drain for removal. As a consequence, the type of post-surgical adhesion "scar" referred to in the '833 reference is not comparable to skin scarring, especially normotrophic scarring.

Furthermore, the Examiner's logic for combining the '833 and '837 references appears to be identical to that for the combination of the '828 and '837 references. Consequently, the arguments presented above are equally valid here and are not repeated.

In view of these discussions taken as a whole, Applicants respectfully request reconsideration and removal of the rejections.

Applicants hereby submit that all of the pending claims, including the newly added claim, define novel, unobvious and patentable subject matter and respectfully request reconsideration of the rejections and allowance of the claims.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), Applicants petition for an extension of one (1) month to September 30, 2007 for the period in which to file a response to the Office Action dated May 31, 2007. The Commissioner is hereby authorized to charge Deposit Account 02-2448 in the amount of $120 for the fee for extension of response within the first month.

Should there be any outstanding matters that need to be resolved in the present application; the Examiner is respectfully requested to contact Susan W. Gorman (Reg. No. 47,604) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Encls.: Wokalek and Ruh (1991, J Biomaterials Applications 5: 338-362
Chapter XXIV Skin Diseases (Frank Parker (1988) pages 2304-2342